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# Quiescent Nasal T/NK Cell Lymphoma Manifested as Primary Central Nervous System Lymphoma

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**A 57-year-old man was diagnosed as primary T/NK-cell central nervous system lymphoma (CNSL) with intraocular involvement. However, review of a surgical specimen taken three years before for chronic paranasal sinusitis revealed an overlooked nasal T/NK cell lymphoma (TNKL), which showed similar histomorphology and immunophenotype with the CNS disease. Another patient, a 43-year-old woman, was initially diagnosed as a rare primary leptomeningeal T-cell lymphoma with ocular manifestation. Three years later, an isolated nasal TNKL emerged. Immunohistochemical and cytogenetic studies confirmed the same nature of the CNSL and the nasal TNKL. The nasal TNKLs of both patients had a strong expression of CD3, CD56, and Epstein-Barr virus antigens, but features of angiodestruction and mucosal ulceration were absent. We propose that: 1. a locally silent ''quiescent'' form of nasal TNKL may exist; and 2. a thorough examination and even blind biopsy of the nasal cavity is indicated when primary T/NK-cell CNSL is diagnosed. Am. J. Hematol. 60:161–163, 1999.** 

**Key words: nasal T/NK cell lymphoma; CNS lymphoma**

## INTRODUCTION

Primary nasal lymphoma is more prevalent in Oriental countries [1]. Most nasal lymphomas are related to malignant T-cell disorders [2]. Recently, it was demonstrated that more than half of these nasal lymphomas expressed natural killer (NK) cell-related markers, such as CD56 and CD16; therefore, the term nasal T/NK-cell lymphoma (TNKL) was proposed [3].

Nasal TNKL frequently involves extranodal sites such as lung, skin, and central nervous system (CNS) [4]. Although CNS metastasis or invasion is not unusual for nasal TNKL (<10%), it always occurs after the diagnosis of primary nasal tumor is well established [5]. To date, there is no report suggesting that nasal TNKL can be locally silent and present as a primary CNS lymphoma.

### Patient No. 1

A 57-year-old man noticed progressive hearing impairment of his right ear and progressive paresthesia accompanied by muscle spasm of his right hand in late 1996. A magnetic resonance imaging (MRI) study revealed multiple lesions primarily involving the white matter of bilateral cerebrum (Fig. 1). Multiple sclerosis was suspected. Gradual deterioration of vision of both eyes was noted in March 1997. Ophthalmologic examination discovered turbid vitreous body, biopsy of which showed large cell lymphoma. Phenotypic examination revealed CD45RO(+), CD3(+), CD56(+), CD19(–), and CD20(–). A stereotactic brain biopsy revealed T/NK cell lymphoma [CD3(+), CD56(+), CD19(–), CD20(–)] with perivascular infiltration. Systemic staging workups including a whole body CT scan and bone marrow studies showed no extra-CNS involvement. Anti-human immunodeficiency virus (HIV) antibody was negative.

Incidentally, review of a prior surgical specimen taken three years before for chronic paranasal sinusitis revealed an overlooked primary nasal lymphoma of identical histomorphology and immunophenotype. The nuclear Ep-

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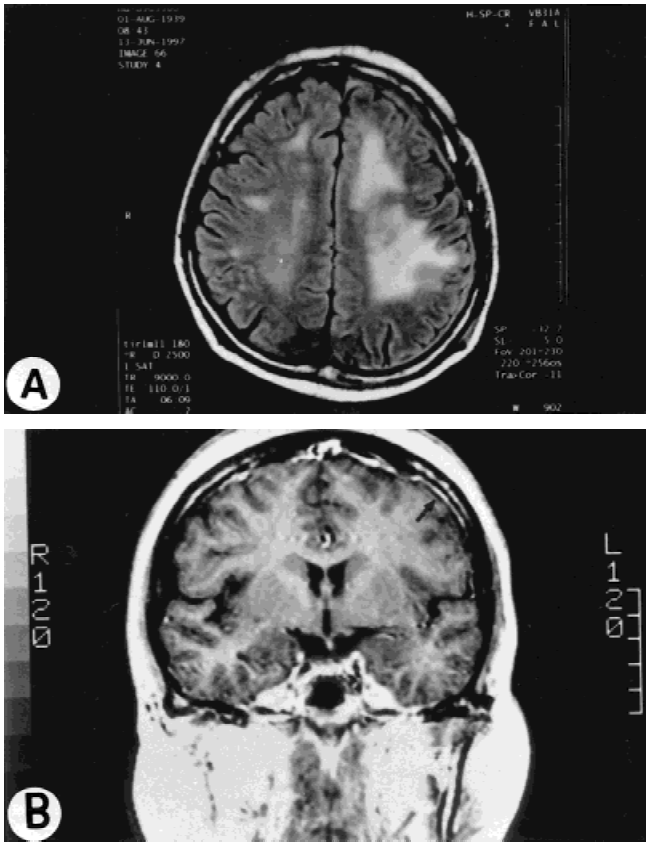


**Fig. 1. Brain MRI of patient no. 1 (A) with lesions mainly in white matter, and patient no. 2 (B) with leptomeningeal enhancement.**

stein-Barr virus (EBV) early region (EBER) RNAs was positive. However, a thorough examination of the nasal cavity and paranasal sinuses revealed no local recurrence. A treatment plan following the protocol of Memorial Sloan-Kettering Cancer Center was initiated on June 14, 1997 [6]. The lymphoma was rapidly progressive and he died on September 20, 1997.

### Patient No. 2

A 43-year-old woman suffered from intermittent headache, blurred vision, and diplopia since late 1992. Rapid deterioration of vision developed in June 1993. A cerebrospinal fluid cytology examination revealed pleomorphic medium-to-large-sized immature lymphoid cells with frequent mitoses [CD3(+), CD7(+), CD19(–), CD20(–)]. Cytogenetic study identified a clonal aberration involving an isochromosome of the long arm of chromosome 7 [i(7q); 45, X, –X, i(7)(q10), der(11) t(1;11)(q21;q21)]. MRI studies showed leptomeningeal enhancement (Fig. 1) and entrapment of the 2nd, 5th, and 7th cranial nerves without parenchymal lesions. Serologic examinations for HIV and EBV were negative. She was successfully treated by an empirical BOMES combination chemotherapy (BCNU, oncovin, methotrexate, etoposide, and solumedrol) that was specifically designed for primary CNS lymphoma [7].

A recurrent tumor arising from the posterior inferior turbinate of her left nasal cavity was noted in December 1995. A partial turbinectomy revealed a pleomorphic large-cell lymphoma [CD45RO(+), CD3(+), CD7(+), CD56(+), CD19(–), CD20(–), nuclear EBER RNAs (+)]. Cytogenetic study revealed [i(7q)] chromosomal changes. The diagnosis was nasal TNKL. Serology of EBV revealed anti-EBV viral capsid antigen IgG 1:1,280(+) and anti-EBV early antigen IgG 1:10(+). She received induction chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisolone) for two courses, followed by high-dose chemotherapy and peripheral blood stem cell support in May 1996. She remained in complete remission until October 1997, when she had recurrent and progressive lymphoma and soon died of the disease.

## DISCUSSION

The CD56 antigen of nasal TNKL corresponds to neural cell adhesion molecule (NCAM), which is characterized by its homophilic binding. The predilection for the nasal TNKL to metastasize to the CNS may partly be explained by the NCAM expression of the brain tissues [8]. However, in patients with nasal TNKL, CNS involvement always occurs concomitantly with locally destructive nasal tumor or with recurrent and wide-spread disease [5]. To date, ''quiescent'' nasal TNKL, presenting as a primary CNS lymphoma, has never been reported.

The diagnosis of patient no. 1 was straightforward. It was surprising to note that the nasal TNKL, which had not been treated either by radiotherapy or chemotherapy, remained locally silent for three years. Even at the time of frank CNS lymphoma, the nasal cavity remained grossly normal.

As for patient no. 2, it may be arguable that the nasal tumor was a recurrent and metastatic lesion from the CNS lymphoma. However, several lines of evidence have strongly suggested that the opposite (i.e., from nasal cavity to CNS) was true. First, nasal T/NK cell lymphoma has been a well-recognized entity, and all reports indicated that it was a primary lymphoma [1]. Second, extra-CNS involvement in patients with primary CNS lymphoma is infrequent (<5%) [9]; and it is even more unlikely for a primary CD56+/EBV+ CNS lymphoma to occur and to metastasize to nasal cavity.

It may be important to point out that the development of nasal TNKL of patient no. 2 was associated with serological evidence of EBV activation. A similar phenomenon has been described in nasopharyngeal carcinoma [10].

Finally, we have noticed that angioinvasion and an-

giodestruction, two of the histologic features commonly seen in nasal TNKL [1], were absent in both of our patients. Whether this absence of angioinvasiveness represents a ''variant'' form and may contribute to the ''quiescent'' nature of the nasal TNKL should be further studied.

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